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10/027,201	12/20/2001	Stephen Quirk	1443.027US1	1416

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EXAMINER	
COUNTS, GARY W	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/027,201	QUIRK, STEPHEN	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04/24/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-18,20-22 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-18,20-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed April 24, 2007 is acknowledged and has been entered. Currently claims 1-5, 7, 9-18, 20-22 and 24 are pending.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

3. Claims 1, 2, 5, 7, 9, 12-18, 20-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohrmann et al (US 6,193,953) in view of Steiner et al (US 4,925,673) and Kayyem et al (US 6,232,295).

Lohrmann et al disclose protein microparticles that can be comprised of chemically synthesized amino acid polymers (col 5, lines 40-57). Lohrmann et al disclose that the microparticles can comprise fluorines or I^{125} (radioisotope)(label) (col

15, lines 1-16). Lohrmann et al also disclose that the microparticles can comprise a targeting moiety such as an antibody linked to the microparticle (col 13, lines 27-29). Lohrmann et al disclose that the microparticles can be used in imaging applications such as MRI (col 15, lines 5-12).

Lohrmann et al differ from the instant invention in failing to specifically state that their protein microparticle is a proteinoid microparticle. Lohrmann et al also differ from the instant invention in failing to teach the label covalently linked to the proteinoid microsphere.

Steiner et al discloses proteinoid microspheres (microparticles). Steiner et al discloses that the proteinoid microspheres are man made condensation polymers produced by random or directed assembly of natural or synthetic amino acids. Steiner et al disclose methods of producing the microspheres by using heat to condense the amino acids (see examples). Steiner et al disclose a mixture of amino acids comprising an acidic amino acid and a basic amino acid (col 5, lines 27-51). Steiner et al disclose that the proteinoid microspheres can comprise a mixture of aspartic acid, glutamic acid, asparagines, arginine and serine amino acids (col 5, lines 29-52). Steiner also teaches that these condensed polymers provide for protein microparticles which are non-toxic and can be very finely tuned for solubility characteristics (col 3) .

Kayyem et al disclose polymeric delivery vehicles that are tissue specific used in MRI applications. Kayyem et al disclose that a contrasting agent (label) is attached (linked) to the polymeric delivery vehicle. Kayyem et al disclose that the label is covalently attached to the polymeric delivery vehicle. Kayyem et al teaches that

gadolinium and fluorine are interchangeable as labels in imaging (col 4). Kayyem et al disclose that this provides for a safe and effective means and for improved targeted delivery of contrast agents to specific cells or tissue (col 2-col 4) and allow for medical imaging.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to synthesize the protein microparticles of Lohrmann et al using condensed amino acids such as taught by Steiner et al because Lohrmann et al specifically teaches that the protein microparticles can be comprised of synthesized amino acid polymers and Steiner et al specifically teaches that proteinoid microspheres are man made condensation polymers produced by random or directed assembly of synthetic amino acids and that these provides for protein microparticles which are non-toxic and can be very finely tuned for solubility characteristics (col 3) . Therefore, one of ordinary skill in the art would have a reasonable expectation of success to form the protein microspheres of Lohrmann et al by condensing amino acids such as taught by Steiner et al. Therefore, the combination of Lohrmann et al and Steiner et al disclose proteinoid microspheres.

It also would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently attach labels to the polymeric surface such as taught by Kayyem et al on the modified protein microparticles of Lohrmann et al because Lohrmann et al specifically disclose that their microparticles can be polymeric (col 5) and used in imaging applications (col 15, lines 5-12) and also comprises labels such as fluorine and further because Kayyem et al teaches that this provides for a safe and

effective means and for improved targeted delivery of contrast agents to specific cells or tissue (col 2-col 4) and allow for medical imaging. Therefore, one of ordinary skill in the art would have a reasonable expectation to attach labels as taught by Kayyem et al on the modified proteinoid microparticle of Lohrmann et al.

With respect to the recitation "and the proteinoid microsphere is stable in solution". Since the combination of the above references teach the same microspheres as recited. The modified microspheres of Lohrmann et al would be stable in solution.

With respect to claims 5 and 13-16 as recited in the instant claims. The claims are directed to intended use of the proteinoid microspheres and therefore are not given patentable weight. Further, since the combination of references disclose the claimed invention and the Applicant has not recited any structural differences over the prior art, the prior art is capable of performing the intended use.

4. Claims 3, 4, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohrmann et al in view of Steiner et al and Kayyem et al and further in view of Mathiowitz et al (US 5,271,961).

See above for the teachings of Lohrmann et al, Steiner et al and Kayyem et al.

Lohrmann et al., Steiner et al., and Kayyem et al differ from the instant invention in failing to teach the proteinoid microsphere is formed by thermal condensation of a mixture of amino acids in the presence of a cross linking agent.

Mathiowitz et al disclose protein microspheres that can be modified. Mathiowitz et al disclose that the modification of the protein can be done by cross-linking the protein using agents such as glutataldehyde (col 6, lines 51-62). Mathiowitz et al

disclose that such modifications provide a protein having enhanced or altered thermal stability, surface reactivity, molecular weight, charge and resistance to proteases (col 5, lines 50-56).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate cross-linking as taught by Mathiowitz et al into the modified microspheres of Lohrmann et al because Mathiowitz et al shows that such modifications provides a protein having enhanced or altered thermal stability, surface reactivity, molecular weight, charge and resistance to proteases.

Response to Arguments

5. Applicant's arguments filed April 24, 2007 have been fully considered but they are not persuasive.

Applicant argues that the combination of references fail to teach a proteinoid microsphere with an external, covalently-linked label. Applicant specifically argues that the Lohrmann and Steiner references are limited encapsulation of contrast agents (e.g. gases and liquids) and pharmacological agents, where none of these gases, liquids or pharmacological agent is covalently attached to any form of the microspheres. Applicant states that Kayyem discloses polymers ionically-associated with paramagnetic control agents. Applicant states that such combined teaching on non-covalently encapsulated air/liquid and polymers ionicallly associated with paramagnetic contrast agents is not a disclosure of a labeled proteinoid microsphere. This is not found persuasive because of reason stated in the previous office actions and further because, while Examiner agrees that Lohrmann and Steiner teaches encapsulation of the agents.

The examiner has not relied upon these references for the teaching of the agent covalently linked to the surface, rather the examiner has relied upon Kayyem for teaching covalent linkage. Also, Lohrmann et al clearly teaches (col 15) that the microparticles can be used in MRI and can comprise fluorine or I^{125} (radioisotope) labels. Also, Examiner has not relied upon Lohrmann et al for teaching the fluorine bound to the surface but rather has relied upon Kayyem et al for teaching that it is known in the art to covalently bind fluorine and gadolinium to polymeric carrier vehicles. Further, as shown above Kayyem et al teaches that gadolinium and fluorine are interchangeable as labels in imaging (col 4). Kayyem et al also teaches that the labels covalently linked to the surface (fig 1 and col 8, lines 50-54).

Applicant argues that Kayyem contrast agents are paramagnetic ions typically associated or complexed with chelating agents (applicant directs Examiners attention to col 5, line 11 to col 6, line 5). Applicant states that there is not covalent linkage between the contrast agents and polymers of Kayyem. This is not found persuasive because Kayyem specifically teaches the covalent linkage of labels (col 8, lines 50-54).

Applicant argues that the present proteinoid microspheres are made by thermal condensation of amino acids, which yields a thermally-stable protease resistant microsphere and that in contrast Lohrmann are made from proteins or chemically synthesized amino acid polymers (i.e. peptide) and unless such protein microspheres are first "metal stabilized" they will be "irreversibly damaged" during heat treatment. This is not found persuasive because it appears that applicant is arguing the references individually. As in the previous office actions the Lohrmann (primary) reference clearly

teaches the microparticle is a protein microparticle and clearly teaches the microparticle is comprised of amino acid polymers (col 5) and also teaches that the microparticles can be heat treated (thermal) (col 16, example 4). Further as stated above it would have been obvious to synthesize the protein microparticles of Lohrmann et al using condensed amino acids such as taught by Steiner et al because Lohrmann et al specifically teaches that the protein microparticles can be comprised of synthesized amino acid polymers and Steiner et al specifically teaches that proteinoid microspheres are man made condensation polymers produced by random or directed assembly of synthetic amino acids and that these provides for protein microparticles which are non-toxic and can be very finely tuned for solubility characteristics (col 3) . Further, the combination of references would use the same amino acids as applicant currently recites see for example claim 24 and Steiner (col 5, lines 29-53). Thus, the modified proteinoid would have the same properties as recited.

Applicant argues that Steiner teaches away from protein and polymer based delivery agents and thus one of skill would have no motivation to combine Lohrmann, Steiner and Kayyem. Applicant directs the examiners attention to col 1, lines 30-38, col 1, lines 39-64 and col 3 lines 27-29. This is not found persuasive because the disclosures applicant argues are directed to embodiments in which the proteinoid is in the digestive tract, and Examiner has not relied upon Steiner for the use of the microparticles but rather as relied upon Steiner for teaching the formation of a protein microsphere using condensed amino acids.

Applicant argues that Lohrmann specifically discloses "chemically synthesized amino acid polymers" (col 5, lines 53-57) and states that such a disclosure that the amino acid polymers are "chemically" synthesized immediately guides one of skill in the art away from any inclination to thermally condense amino acids. This is not found persuasive because Lohrmann et al also explicitly teaches that the microparticles can be heat treated (thermal) (col 16, example 4). Therefore, one of ordinary skill in the art would not be guided away from any inclination of thermal treatment.

Applicant argues that Mathiowitz is limited to use of a crosslinker for chemical modification of a protein and discloses nothing about thermal condensation of a mixture of amino acids to form proteinoid microspheres while suing a crosslinking agent. Applicant states that in contrast to the presently claimed invention, the crosslinkers of Mathiowitz are used to modify the charge of a protein before the protein microspheres are made. First, the Examiner has not relied upon Mathiowitz for teaching thermal condensation of a mixture of amino acids but rather has relied upon Mathiowitz for teaching that it is known in the art to cross-link amino acids (col 6) and that this cross-linking provides for a protein having enhanced or altered thermal stability, surface reactivity, molecular weight, charge and resistance to proteases (col 5). Second, with respect to the argument of the formation of the protein microspheres, this is not found persuasive because the current claims are not directed to methods of making proteinoid microspheres but rather are directed to the proteinoid microsheres thus the argument is not on point. As stated above the claims are directed to products and not methods of making the product. Thus, determination of patentability is based on the product itself

and the patentability of a product does not depend on its method of production. If the product in a product by process claim is the same or obvious from a product in the prior art then the claim is unpatentable.

Applicant further argues that Mathiowitz disclosure is limited to protein delivery systems and that Steiner teaches away from use of such protein, thereby providing no motivation for combining Steiner with Mathiowitz. This is not found persuasive because of reasons stated above and in the prior office actions that Steiner does not teach away and further because the rejection is not based on the mere combination of Steiner and Mathiowitz but rather is based on the combination of Primary reference Lohrmann in view of Steiner, Kayyem and Mathiowitz. Thus, it appears that applicant is arguing the references individually and not as a whole.

Applicant argues that Mathiowitz teaches away from forming microspheres under harsh conditions and would discourage one of skill in the art from forming microspheres pursuant to the present invention. This is not found persuasive because the examiner has not relied upon Mathiowitz for teaching the formation of microsphere but has relied upon Mathiowitz for teaching that it is known in the art to cross-link amino acids and that this cross-linking provides for a protein having enhanced or altered thermal stability, surface reactivity, molecular weight, charge and resistance to proteases.

Applicant also argues that Mathiowitz fails to disclose external labeling of a microsphere and teaches only the incorporation of compounds into the microspheres. This is not found persuasive because the examiner has not relied upon Mathiowitz for

teaching these limitations but rather upon Kayyem for teaching external labeling and its advantages.

Conclusion

6. No claims are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gary Counts
Examiner
Art unit 1641
June 21, 2007

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